



# STAT1 contributes to HLA class I upregulation and CTL reactivity after anti-EGFR mAb cetuximab therapy in head and neck cancer patients

## Citation

Srivastava, Raghvendra M, Hyun-bae Jie, Soldano Ferrone, and Robert L Ferris. 2013. "STAT1 contributes to HLA class I upregulation and CTL reactivity after anti-EGFR mAb cetuximab therapy in head and neck cancer patients." *Journal for Immunotherapy of Cancer* 1 (Suppl 1): P175. doi:10.1186/2051-1426-1-S1-P175. <http://dx.doi.org/10.1186/2051-1426-1-S1-P175>.

## Published Version

doi:10.1186/2051-1426-1-S1-P175

## Permanent link

<http://nrs.harvard.edu/urn-3:HUL.InstRepos:12407007>

## Terms of Use

This article was downloaded from Harvard University's DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at <http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA>

## Share Your Story

The Harvard community has made this article openly available.  
Please share how this access benefits you. [Submit a story](#).

[Accessibility](#)

POSTER PRESENTATION

Open Access

# STAT1 contributes to HLA class I upregulation and CTL reactivity after anti-EGFR mAb cetuximab therapy in head and neck cancer patients

Raghvendra M Srivastava<sup>1\*</sup>, Hyun-bae Jie<sup>1</sup>, Soldano Ferrone<sup>4</sup>, Robert L Ferris<sup>1,2,3</sup>

From Society for Immunotherapy of Cancer 28th Annual Meeting  
National Harbor, MD, USA. 8-10 November 2013

Squamous cell carcinoma of head and neck (HNSCC) cells express low HLA class I and antigen processing machinery (APM) components, such as transporter TAP-1/2, which is associated with the reduced sensitivity to cytotoxic T lymphocyte (CTL) mediated lysis. Epidermal growth factor receptor (EGFR) is overexpressed in HNSCC and is associated with the poor prognosis. FDA approved anti-EGFR blockade mAb cetuximab inhibits HNSCC proliferation, and induces EGFR-specific CTL. However, the molecular mechanism(s) underlying the EGFR-specific CTL recognition of HNSCC in the therapeutic efficacy of anti-EGFR mAb is still emerging. We show that cetuximab or EGFR knockdown enhanced expression of HLA class I antigens, which is associated with the EGFR expression level on HNSCC. These findings were validated in a prospective trial of neoadjuvant cetuximab therapy. Interestingly, upregulation of HLA-B/C alleles were more pronounced than HLA-A alleles after cetuximab or EGFR knockdown treatment. EGFR signaling blockade or EGFR depletion also enhanced IFN gamma receptor (IFNAR) on HNSCC and augmented induction of HLA class I and TAP-1/2 caused by IFN gamma treatment. Cetuximab or EGFR knockdown enhanced the level of HLA class I, STAT-1, TAP-1/2 in a STAT-1+/+ cell line but not in STAT-1-/- cell line, documenting the STAT-1 dependence of this effect. We also found that Src homology domain-containing phosphatase 2 (SHP-2), which is downstream of EGFR and also overexpressed in SCCHN, can suppress the immunostimulatory effect of cetuximab treatment on HLA class I/STAT-1 upregulation, and dual targeting of EGFR and SHP-2 co-operates in the most efficient reversal of

immune escape phenotype. In addition, cetuximab-based EGFR inhibition and SHP-2 depletion enhanced the recognition of HNSCC cells by EGFR<sub>853-861</sub> specific CTL, and enhanced surface presentation of non-EGFR TA, such as MAGE-3<sub>271-279</sub>, indicating that a broad tumor antigen repertoire is processed and presented by HLA/APM upregulation. These findings elucidate a novel immune escape mechanism associated with EGFR signaling through STAT1 suppression and the reversal with cetuximab, which may provide additional targets for on-going mAb-based immunotherapy.

## Authors' details

<sup>1</sup>Department of Otolaryngology, University of Pittsburgh, Pittsburgh, PA, USA.

<sup>2</sup>Department of Immunology, University of Pittsburgh, Pittsburgh, PA, USA.

<sup>3</sup>Cancer Immunology Program, University of Pittsburgh, Pittsburgh, PA, USA.

<sup>4</sup>Department of Surgery, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA.

Published: 7 November 2013

doi:10.1186/2051-1426-1-S1-P175

**Cite this article as:** Srivastava et al.: STAT1 contributes to HLA class I upregulation and CTL reactivity after anti-EGFR mAb cetuximab therapy in head and neck cancer patients. *Journal for ImmunoTherapy of Cancer* 2013 **1**(Suppl 1):P175.

<sup>1</sup>Department of Otolaryngology, University of Pittsburgh, Pittsburgh, PA, USA  
Full list of author information is available at the end of the article